CERTIFICATE OF ELECTRONIC TRANSMISSION
I hereby certify that this paper is being electronically transmitted on May 12, 2008 (Date of Deposit)
May 12, 2008 /Manette Dennis/
Manette Dennis (Reg. No. 30,623)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Serial No. : 10/524,065 **Confirmation No. :** 4447

First Named Inventor: Takaya Sugawara

Filing or 371(c) Date: February 8, 2005 **Customer No. :** 44702

Art Unit: 1615 **Examiner:** Suezu Y. Ellis

Title: FEMALE HORMONE-CONTAINING PATCH

Attorney Docket No. : KPO-TSC-P1/TK-80/US

AMENDMENT

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In response to the Office Action of December 11, 2007, please amend the above-identified application as follows:

Amendments to the Claims are reflected in the listing of claims, which begins on page 2 of this paper.

Remarks/Arguments begin on page 4 of this paper.

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

Claims 1-5. (Canceled)

6. (New) An external patch comprising a backing and a pressure-sensitive adhesive layer, wherein the backing is a laminate structure comprising a polyethylene terephthalate film having a thickness of 0.1 to 10 μm, a flexible polymer film and a non-woven or woven fabric having a thickness of 1 to 200 μm; and wherein the pressure-sensitive adhesive layer is made of an acrylic pressure-sensitive adhesive, wherein the adhesive layer further comprises:

0.01 to 1% by weight of an isocyanate-based crosslinking agent;

0.5 to 10% by weight of estradiol and/or a derivative of estradiol as an active ingredient;

0.5 to 10% by weight of crotamiton; and

0.1 to 10% by weight of oleic acid.

7. (New) An external patch comprising a backing and a pressure-sensitive adhesive layer, wherein the backing is a laminate structure comprising a polyethylene terephthalate film having a thickness of 0.1 to 10 μm, a flexible polymer film and a non-woven or woven fabric having a thickness of 1 to 200 μm; and wherein the pressure-sensitive adhesive layer is made of an acrylic pressure-sensitive adhesive, wherein the adhesive layer further comprises:

0.01 to 1% by weight of an isocyanate-based crosslinking agent;

1 to 30% by weight of isopropyl myristate as a distribution coefficient control agent; and

0.5 to 10% by weight of norethisterone and/or a derivative of norethisterone as an active ingredient.

8. (New) The external patch according to claim 6 or 7, wherein the flexible polymer film is low density polyethylene film.

9. (New) The external patch according to claim 6 or 7, wherein the pressure-sensitive adhesive is a acrylic pressure-sensitive adhesive comprising at least one of the following compounds: 2-ethylhexyl acrylate, acrylic acid, ethyl acrylate, vinyl acetate, and an acrylic ester.

REMARKS/ARGUMENTS

Claims 1-5 were cancelled. New Claims 6-9 are pending after this amendment.

Re. Features of the present invention

1. The present invention relates to an external patch comprising a backing and a pressure-sensitive adhesive layer, wherein the backing is a laminate structure comprising a polyethylene terephthalate film, a flexible polymer film, and a non-woven or woven fabric; and the pressure-sensitive adhesive layer is made of an acrylic pressure-sensitive adhesive containing 0.01 to 1% by weight of an isocyanate-based crosslinking agent and contains 0.5 to 10% by weight of a female hormone as an pharmaceutically active ingredient.

The present invention provides a female hormone-containing patch wherein the pharmaceutically active ingredient is highly soluble in a pressure-sensitive adhesive layer and the pharmaceutically active ingredient is not absorbed to a backing. The patch per se is very flexible and can conform to irregularities on the skin surface and to body movements.

By using the laminate structure comprising a drug non-absorptive layer having a very thin and dense structure and a flexible film capable of following the irregularities on the skin or body movements as a backing, it is possible to prevent the absorption of the active ingredient to the backing, and thereby improving the transdermal absorbability of a drug.

For these purposes, in the present invention, the polyethylene terephthalate film is used as drug non-absorptive layer, and laminated with flexible polymer film, and a non-woven or woven fabric to consist the backing layer.

These specific features are well demonstrated in the Test Examples 3 and 6, and the unexpected superior effects are shown in Figures 7 to 9, and 12 to 15 of the present specification.

2. In the case of using estradiol and/or its derivative as an active ingredient, 0.1 to 10% by weight of crotamiton, and 0.1 to 10% by weight of oleic acid are contained as a solubilising agent for the active ingredient, and the unexpected high drug releasing effect is obtained as shown in the Test Example 1 and Figure 2.

Further, in the case of using norethisterone and/or its derivative as an active ingredient isopropyl myristate as a distribution coefficient control agent, and the unexpected high drug releasing effect is obtained as shown in the Test Example 4 and Figure 10.

These superior effects of the present invention are not described or suggested in the cited references.

Claim Rejections – 35 USC § 103

Claims 1-2 were rejected under 35 U.S.C. 103(a) as being unpatentable over Akemi et al. Claim 3 was rejected under 35 U.S.C. 103(a) as being unpatentable over Akemi et al. in view of Yamaguchi et al. Claim 4 was rejected under 35 U.S.C. 103(a) as being unpatentable over Xia et al. in view of Hoffman et al. Claim 1/5 and 2/5 were rejected under 35 U.S.C. 103(a) as being unpatentable over Akemi et al. in view of Xia al. Claims 1to 5 are cancelled in the present amendment and therefore the specific rejections are no longer relevant. However, in order to facilitate the prosecution of the application, applicants offer the following comments regarding the references.

Re: Akemi et al. (US 5,242,951)

1. Akemi et al. disclose "an estrogen-containing gel preparation which is to be applied to the surface of the skin so as to continuously administer estrogen to the living body via the skin surface." (Col. 1, lines 5-8 of Akemi et al.) This "estrogen-containing gel preparation comprises a substrate having on one surface thereof a

crosslinked gel layer formed by crosslinking a composition comprising the following ingredients (a) to (c), the weight ratio of the ingredient (b) to the ingredient (c) being from 1/0/0.25 to 1.0/2.0:

(a) Estrogen;

(b) An acrylate polymer; and

(c) A liquid ingredient compatible with the ingredient (b)." (Col. 2, lines 9-19 of Akemi et al.)

The substrate selected in the Akemi et al. reference should "never suffer from any decrease in the content of the liquid ingredient or the estrogen contained in the crosslinked gel layer caused by the migration toward another surface of the substrate followed by leakage." (Column 2, line 29 to 36). Examples include sole film of polyester, nylon, polyethylene and so on, as well as laminated film thereof. (Col. 2, lines 36 -41). To improve the adhesiveness between the substrate and the crosslinked gel layer by the anchoring effect, substrate in the form of laminate films composed of a nonporous sheet comprising one or more materials and a porous film and to form a crosslinked gel layer on the surface of the porous film and to form a crosslinked gel layer on the surface of the porous sheet (column 2, line 41 to 49).

However, Akemi et al. does not describe or suggest the using of the polyethylene terephthalate film as drug non-absorptive layer, further laminated with flexible polymer film and a non-woven or woven fabric to consist the backing layer of the present invention, as well as the unexpectedly, superior effect of the present invention.

2. In Akemi et al., it is suggested that the crosslinked gel layer containing estrogen is composed on the surface of the porous sheet. On the contrary, in the present invention, the drug non-absorptive layer is a very thin layer composed on the surface of backing.

3. In Akemi et al., a liquid ingredient (c) compatible with the ingredient (b) is used. This liquid ingredient (c) moderately plasticizes the crosslinked gel layer and thus imparts a flexible texture, in order to thereby relieve pain or skin irritation caused by the skin adhesiveness upon the separation of the crosslinked gel layer from the skin surface.

The examples of the liquid ingredient (c) include fats and oil such as olive oil; organic solvents such as dimethyl decyl sulfoxide; liquid surfactants; plasticizers such as diisopropyl adipate; hydrocarbons such as liquid paraffin; glycerol astes; or 1, 3-butandiol. Isopropyl myristate and oleic acid are described as the liquid ingredient; *however, these materials act are as plasticizers for the crosslinked gel layer, and* ***not*** *a* ***solubilising*** *agent for the active ingredient as in the present invention.*

Furthermore, in the present invention, isopropyl myristate is used as a distribution coefficient control agent.

Additionally, the superior efficacy achieved by the patches according to the present invention are not at all described or suggested in Akemi et al.

In the Official Action, the Examiner pointed that Akemi et al. fails to expressly disclose the isocyanate-base crosslinking agent being 0.01-1% by weight, however Akemi et al. does teach using isocyanate-based crosslinking agent used in an amount from 0.01 to 2.0 parts by weight per 100 parts by weight of acrylate polymer. Applicants respectfully maintain that it would not have been obvious to one of ordinary skill in the art to modify the amount of isocyanate-based crosslinking agent. There would have been no reason to change the amounts suggested by Akemi et al. sufficiently to be used in the teaching of the present invention since Akemi et al,'s use of these agent is so different.

In summary, in Akemi et al., the liquid ingredient (c) must be compatible with the ingredient (b). This liquid ingredient (c) moderately plasticizes the crosslinked gel

layer and thus imparts some flexibility to relieve pain or skin irritation when the gel preparation taught by Akemi et al. is removed from the skin. Further, the Akemi et al. fails to expressly disclose an isocyanate-based crosslinking agent, the use of an isocyanate-based crosslinking agent as a solubilising agent, or the amount of isocyanate-based crosslinking agent that would be useful as a solubilising agent as taught in the present invention.

Applicants respectfully submit that the claims are not obvious in view of Akemi et al., separately or in combination with the other cited references.

Re: Yamaguchi et al. (US 5,820,877)

1. The preparation of Yamaguchi et al. includes: "(1) a backing layer impermeable to a drug component, (2) a drug storage layer which holds the drug component therein and is situated under the central portion of the backing layer, (3) a protective film which is impermeable to the drug component, has notches and is situated under the drug storage layer and the peripheral portion of the backing layer, (4) a pressure-sensitive adhesive layer which is situated under the protective film, and (5) a releasable liner layer which is impermeable to the drug component and situated under the pressure-sensitive layer." See Abstract. As such, the Yamaguchi et al. disclosure isolates the drug preparation away from the pressure-sensitive adhesive layer. There is no interaction or influence between the active ingredient and the adhesive layer. Therefore, the invention of Yamaguchi et al. is clearly different from the present invention.

Re: Xia et al. (US. 5,693,335)

1. The Xia et al. reference relates to a skin preparation enhancer composition for increasing the permeability of skin to sex steroids.
The Xia et al. reference uses polyhydric thioalcohol of 2 to 6 carbon atoms having at least one mercapto group and at least one hydroxy group and an aliphatic carboxylic acid of 8 to 24 carbon atoms or ester thereof. In the present invention, only oleic acid

is used as a solubilising agent for the active ingredient, and therefore, is quite different from the invention of Xia et al.

2. In Xia et al., a single layer or film of polymer, or a laminate of one or more polymer layer and metal foil is used as backing layer, not a laminate structure The present invention teaches a backing which is a laminate structure comprising a polyethylene terephthalate film having a thickness of 0.1 to 10 μm and a flexible polymer film, a non-woven fabric, or a woven fabric having a thickness of 1 to 200 μm of the present invention is not described or suggested in Xia et al.

Re: Hoffman et al. (US 5,393,529)

1. The invention of Hoffman et al. relates to an active substance containing plaster for the controlled release of active substances to the skin consisting of a backing layer being impermeable to the active substance(s), and removable protective layer, for transdermal application of estrogens, their pharmaceutically acceptable derivatives alone or in combination with gestagens in human medicine.

In the invention of Hoffman et al., water-swellable polymer has to be used in combination with estrogen. No water-swellable polymers are used or needed in connection with the present invention.

Applicants respectfully submit that new claims 6-9 are patentable and in condition for allowance.

CONCLUSION

If the Examiner has any questions or suggested Examiner's amendments, the Examiner is respectfully requested to call the undersigned.

The Commissioner is hereby authorized to charge any additional fees, or to credit any overpayment, to Deposit Account No. 50-3195.

.

Respectfully submitted,

Date: May 12, 2008

/Manette Dennis/

Manette Dennis (Reg. No. 30,623)
Ostrager Chong Flaherty & Broitman P.C.
570 Lexington Avenue, Floor 17
New York, NY 10022-6894
Tel.: 212 681-0600
Fax: 212 681-0300
mdennis@ocfblaw.com